

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Complete Specification, Abstract & Drawings of the extract of Patent Application No.637/MAS/2002, dated 30.08.2002 by Dr. Reddy's Laboratories Limited having its registered office at 7-1-27, Ameerpet, Hyderabad 500 016, Andhra Pradesh, India.

.....


.....In witness thereof

I have hereunto set my hand

Dated this the 7th day of November 2003
16th day of Kartika, 1925(Saka)


(K.M. VISWANATHAN)

ASSISTANT CONTROLLER OF PATENTS & DESIGNS


PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 6th Floor, Annex.II
No.443, Anna Salai, Teynampet, Chennai – 600 018

Received Rs 5000/- in Cash
Cheque/M.O./P.O./D.D/ on 30/8/02
Vide C.B.R. No. 4545. Inv 02
30/8/02

FORM 1

THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7 and Rule 33A)

We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare

- (a) that we are in possession of an invention titled "**Novel forms of (S)-Repaglinide and process for preparation thereof**"
 - (b) that the complete specification relating to this invention is filed with this application.
 - (c) that there is no lawful ground of objection to the grant of a patent to us.
1. further declare that the inventors for the said invention are **Manne Satyanarayana Reddy, Sajja Eswaraiah, Vijayavithal Thippannachar Mathad, Govindan Shanmugam, Maddipatla Madhavi and Kolla Naveen kumar**. All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad - 500 016, Andhra Pradesh**.
 2. that we are the assignee of the true and first inventors
 3. that our address for service in India is as follows;
Dr. M. Satyanarayana Reddy,
Vice President
Dr. Reddy's Laboratories Limited
7-1-27, Ameerpet
Hyderabad, A.P., 500 016
 5. following declaration was given by inventors.
We, the true and first inventors for this invention declare that the applicant herein is our assignee.

Signed) _____


Manne Satyanarayana Reddy,
H.No: 8-3-167/D/16,
Kalyan Nagar
Near AG Colony
Erragadda
Hyderabad- 500 038

Signed) _____

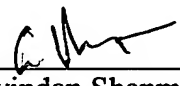
Sajja Eswaraiah,
LIG 100,
Dharma Reddy Colony,
K.P.H.B Colony,
Kukatpally,
Hyderabad - 500 072.

ORIGINAL 30 AUG 2002 637 MAS 2002

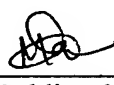
Signed) _____


Vijayavithal Thippannachar Mathad,
Flat No: 114, Adithya homes,
Adithya Nagar, opp. JNTU,
Pragathi Nagar Road,
Kukatpally,
Hyderabad-500 072.

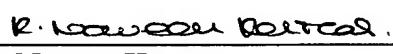
Signed) _____


Govindan Shanmugam
HIG-64, Bharat Ngr Colony
Hyderabad-500 018

Signed) _____


Maddipatla Madhavi,
B-393; LIG
Dr A S Rao Nagar
ECIL
Hyderabad-500 062

Signed) _____


Kolla Naveen Kumar,
L.I.G, 957/1, flat No: 102,
Manoja buildings, III phase,
K.P.H.B Colony,
Hyderabad-500 072.

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application
7. following are the attachments with the application
- (a) complete specification (~~---20---~~ ²⁰ pages, in triplicate)
 - (b) abstract of the invention (~~---01---~~ ⁰¹ page, in triplicate)
 - (c) drawings (~~---04---~~ ⁰⁴ pages, in triplicate)
 - (d) fee Rs. 5000.00 (five thousand rupees only) in Cheque vide No "739070" dated August 12th drawn on HDFC Bank, Lakdikapool, Hyderabad- 500 004.

We request that a patent may be granted to us for the said invention

Dated this 28th day of August 2002.

(Signed)



Dr. M. Satyanarayana Reddy,
Vice President
Dr. Reddy's Laboratories Limited.

To,
The Controller of Patents
The Patents Office Branch, Chennai.

FORM-2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(SECTION 10)

**Novel forms of (S)-Repaglinide and process for preparation
thereof**

**Dr. Reddy's Laboratories Limited,
An Indian Company having its registered office at
7-1-27, Ameerpet,
Hyderabad-500 016, A.P., India.**

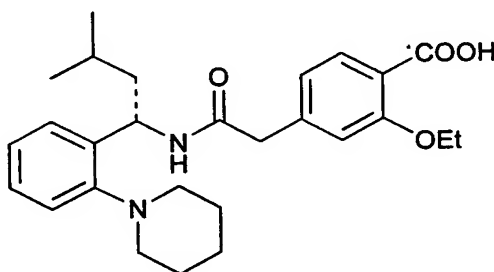
The following specification particularly describes the nature of this invention and the manner on which it is to be performed.

ORIGINAL
30 AUG 2006 37
TAS 2006

FIELD OF THE INVENTION:

The present invention relates to novel forms of (S)- Repaglinide.

More specifically, the present invention relates to novel crystalline Form-III and novel amorphous form of (S)- Repaglinide. The present invention also relates to processes for the preparation thereof. Chemically (S)-Repaglinide is (S)-2-Ethoxy-4- [N- (1-(2-piperidino-phenyl)-3-methyl-1-butyl)-amino carbonyl methyl] benzoic acid having the following formula:



BACK GROUND OF THE INVENTION:

Repaglinide is an anti diabetic drug used as therapeutic agent for type-2 diabetic patients.

USP 5,216,167 claimed Repaglinide, its enantiomers, pharmaceutically acceptable salts and claimed the crystalline forms namely Form-A, Form-B and Form-C of Repaglinide.

The patent also disclosed the processes for the preparation of Repaglinide, its enantiomers, related compounds, the polymorphic forms and inter-conversion of polymorphic forms. The crystalline forms of Repaglinide are characterized by their IR spectra and visual melting point.

The solvents used in the crystallization process and their melting points are described below:

- **Form-A:** Repaglinide recrystallised from Acetone / Petroleum ether having a melting range of 90-92°C.
- **Form B:** Repaglinide recrystallised from ethanol / water having a melting range of 140-142°C.
- **Form C:** Repaglinide recrystallised from methanol having a melting range of 74-85°C.

The '167 patent claimed the (S)-Repaglinide, its polymorphic forms and their pharmaceutically acceptable salts. The patent also disclosed the preparation of (S)-Repaglinide, which comprises the resolution of racemic 3-methyl-1- (2-piperidino-phenyl)-1-butyl amine with N-acetyl-L-glutamic acid to afford the (S)-enantiomer of corresponding amine. The resultant amine was reacted with 3-ethoxy-4-ethoxy carbonyl-phenyl acetic acid to give ethyl ester of (S)-Repaglinide. The ethyl ester of (S)-Repaglinide on saponification and further recrystallisation in solvent mixture of petroleum ether / toluene yielded the (S) – Repaglinide with melting point 102-104°C (low melting form, which is designated as Form-II for convenience by the inventors of the present invention).

USP 5,312,924 disclosed the preparation of (S)-Repaglinide by the hydrolysis of corresponding ethyl ester. Melting point of (S)-Repaglinide after recrystallization with ethanol / water was found to be 130-131°C (high melting form, which is designated as Form-I for convenience by the inventors of the present invention). This when further recrystallised in petroleum ether / toluene yielded (S)-Repaglinide with melting point 99-

101°C (low melting form, designated as Form-II for convenience by the inventors of the present invention). The crystalline forms of Repaglinide and (S)-Repaglinide are characterized by their IR spectra.

The inventors of the present invention have prepared crystalline forms of (S)-Repaglinide by crystallizing (S)-Repaglinide from the solvent mixture of acetone / petroleum ether or ethanol / water. The crystalline forms obtained by the said crystallization processes were found to be substantially identical when characterized by X-ray diffractogram. The said crystalline form is herewith designated as crystalline Form-I of S-Repaglinide.

The 2 θ values and the relative intensity percentages of the crystalline Form-I of (S)-Repaglinide obtained by the inventors of the present invention are furnished in the following Table-1.

Table-1

FORM – I of (S)-Repaglinide			
Acetone/Petroleum Ether process		Ethanol/water process	
2-Theta	Intensity %	2-Theta	Intensity %
7.58	100	7.60	100
10.06	61.1	10.08	67.6
12.40	2.0	12.40	1.9
12.98	9.5	13.02	9.4
13.21	15.9	13.22	17.3
13.75	25.2	13.76	27.5
14.56	7.5	14.58	7.5
15.26	7.0	15.28	6.7
15.53	1.1	15.53	1.0
16.65	31.7	16.66	33.7
16.94	3.7	16.94	3.9
17.51	8.4	17.53	8.8
18.56	12.4	18.58	12.5
20.26	58.5	20.27	62.4
20.48	19.3	20.52	21.6
21.37	0.8	21.41	0.9
21.88	1.2	21.89	1.3

22.94	25.4	22.93	24.8
23.35	5.3	23.35	7.4
23.95	19.7	23.96	20.2
25.02	1.6	24.99	1.1
25.36	2.4	25.33	2.2
25.66	4.2	25.67	4.1
26.23	3.5	26.25	3.8
26.65	8.4	26.65	9.3
27.75	7.9	27.76	8.4
28.73	0.9	28.73	1.1
29.47	1.1	29.46	1.7
29.77	2.8	29.77	2.9
30.86	15.3	30.88	16.7
31.61	1.3	31.56	1.0
32.49	0.8	32.49	0.9
35.46	1.4	35.46	1.1
36.09	0.9	36.07	1.1
37.02	1.8	37.04	1.9
38.84	1.8	38.89	2.4
39.48	1.1	39.49	1.0
43.55	1.1	43.52	1.0
44.08	1.1	44.09	0.9

Since polymorphic forms of drug substances are known to differ in their physical properties such as melting point, solubility, chemical reactivity etc., they can appreciably influence the pharmaceutical properties such as dissolution rate and bioavailability. Repaglinide and its enantiomers are known to exist in different polymorphic forms. Repaglinide being an anti diabetic drug, used as therapeutic agent for type-2 diabetic patients, it is important to further evaluate the polymorphism to obtain newer polymorphs exhibiting different dissolution characteristics and in some cases superior bioavailability and consequently show much higher activity compared to other polymorphs.

Hence, the present invention aims to provide a novel crystalline Form-III and a novel amorphous form of (S)-2-Ethoxy-4- [N- (1-(2-piperidino-phenyl)-3-methyl-1-butyl)-amino carbonyl methyl] benzoic acid [(S)- Repaglinide].

The novel crystalline Form-III and the novel amorphous forms of the present invention are free flowing and non-solvated compounds and hence may be useful in the preparation of pharmaceutical formulations.

The processes of the present invention are simple, non-hazardous and commercially viable for preparing the same.

SUMMARY OF THE INVENTION:

The present invention is directed to novel crystalline Form-III and novel amorphous form of (S)-Repaglinide and to simple, non-hazardous and commercially viable processes for preparation thereof. The process for preparation of crystalline Form-III comprises dissolution of (S)-Repaglinide crude, (S)-Repaglinide crystalline Form-I, (S)-Repaglinide Form-II or (S)-Repaglinide amorphous in a C₁-C₃ haloalkane solvent at an ambient temperature followed by diluting with an excess volume of a C₅-C₁₀ aliphatic or alicyclic hydrocarbon solvent under stirring to isolate the desired novel crystalline Form-III of (S)-Repaglinide.

The C₁-C₃ haloalkane solvent is selected from dichloromethane, 1,2-dichloroethane and chloroform, preferably dichloromethane. The C₅-C₇ aliphatic or alicyclic hydrocarbon solvent is selected from petroleum ether, hexane, n-heptane, cyclohexane or cyclo heptane, preferably petroleum ether.

The process for preparation of novel amorphous form of (S)-Repaglinide comprises the recrystallisation of crystalline Form-I, Form-II and Form-III of (S)-Repaglinide in C₁-C₄ straight or branched chain alcohol solvent.

The C₁-C₄ straight or branched chain alcohol solvent is selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol and tertiary butanol, preferably methanol.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS:

Fig. 1 is X-ray powder diffractogram of novel crystalline Form-III of (S)-Repaglinide.

Fig. 2 is Differential Scanning Calorimetry thermogram of novel crystalline Form-III of (S)-Repaglinide.

Fig. 3 is Infra red spectra of novel crystalline Form-III of (S)-Repaglinide.

Fig. 4 is X-ray powder diffractogram of novel amorphous form of (S)-Repaglinide.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention is directed to the novel crystalline Form-III and novel amorphous form of (S)-Repaglinide and processes for the preparation thereof.

The process for the preparation of novel crystalline Form-III of (S)-Repaglinide comprises;

- i. dissolving (S)-Repaglinide in C₁-C₃ haloalkane solvent;
- ii. adding C₅-C₇ aliphatic or alicyclic hydrocarbon solvent as anti-solvent to the solution of step (i) to precipitate the solid;
- iii. isolating the precipitated solid obtained in step (ii) to afford the novel crystalline Form-III of (S)- Repaglinide.

The C₁-C₃ haloalkane solvent is selected from dichloromethane, 1,2-dichloroethane and chloroform, preferably dichloromethane. The C₅-C₇ aliphatic or alicyclic hydrocarbon solvent is selected from petroleum ether, hexane, n-heptane, cyclohexane or cyclo heptane, preferably petroleum ether.

The novel crystalline Form-III of (S)-Repaglinide obtained as per the above process is found to be free flowing and non-solvated crystalline solid and is well suited for pharmaceutical applications.

The novel crystalline Form-III of (S)-Repaglinide is characterized by XRD, which shows well-resolved peaks and the diffractogram is substantially as depicted in Figure (1).

The characteristic peaks (in 2-theta values) and their relative intensities (in percentage) are given in the following Table (2).

Table-2:

Form-III of (S)-Repaglinide	
2θ(°)	Intensity (%)
7.803	100.00
19.251	34.10
13.464	31.70
21.185	31.00
4.438	29.20
12.918	28.00
19.995	23.20
19.594	22.60
20.339	22.10
18.060	20.80
22.180	18.40
15.766	17.40
17.081	17.20
9.277	14.60
14.342	11.80
18.747	11.60
23.767	8.80
25.315	7.20

22.581	7.10
11.091	6.80
11.888	6.80
24.080	6.30
25.020	4.40
30.255	3.90
23.235	3.60
28.028	3.20
16.236	3.00
25.780	3.00
6.811	2.70
26.675	2.60
27.388	2.20
35.500	2.20
38.739	2.10

The novel crystalline Form-III of (S)-Repaglinide has also been characterized by DSC, which exhibits a significant endo peak around 80°C.

The Differential scanning calorimetry thermogram of novel crystalline Form-III of (S)-Repaglinide is substantially as depicted by Figure (2).

The novel crystalline Form-III of (S)-Repaglinide of present invention has been further characterized by IR, which is measured by KBr-transmission method. The Infra red spectrum of the crystalline Form-III of (S)-Repaglinide is substantially as depicted in Figure (3).

The identified significant IR bands are around 3291, 3029, 2935, 2795, 1292, 1727, 1643, 1611, 1537, 1436, 1225, 1171, 1087, 1028, 986, 922, 860, 764, 686 and 533 cm⁻¹.

Another aspect of the present invention is to provide a process for the preparation of novel amorphous form of (S)-Repaglinide.

Accordingly the process for the preparation of novel amorphous form of (S)-Repaglinide comprises of

- a) dissolving crystalline form of (S)-Repaglinide in C₁-C₄ straight or branched chain alcoholic solvents at a temperature of 35-70 °C, preferably at 45-55 °C;
- b) cooling the reaction solution of step (a) to a temperature of 0-5 °C;
- c) stirring the reaction solution of step (b) till the solid substantially separates;
- d) filtering the separated solid obtained in step (c) by conventional methods;
- e) drying the resulting solid of step (d) under vacuum at a temperature of 40 to 70°C to a constant weight to afford the desired novel amorphous form of (S)- Repaglinide.

The C₁-C₄ straight or branched chain alcohol solvent is selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol and tertiary butanol, preferably methanol.

The novel amorphous form of (S)-Repaglinide obtained as per the above process is found to be free flowing and non-solvated and thus well suited for pharmaceutical applications.

The present invention of novel amorphous form of (S)-Repaglinide is characterized by X-ray powder diffractogram. The X-ray powder diffraction pattern of novel amorphous form of (S)-Repaglinide of the present invention is measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The X-ray powder diffractogram of novel amorphous form of (S)-Repaglinide obtained in the present process is substantially as depicted in Figure (4).

Thus, the present invention embodies novel crystalline Form-III, amorphous form of (S)-Repaglinide and a process for their preparation.

(S)-Repaglinide crude is prepared as per the process disclosed in US 5,216,167 and US 5,312,924.

(S)-Repaglinide Form – I is obtained either by crystallizing crude (S)-Repaglinide from Ethanol/water as disclosed in USP '924 or by crystallizing crude (S)-Repaglinide from acetone/petroleum ether.

(S)-Repaglinide Form-II is obtained by crystallizing crude (S)-Repaglinide from toluene/petether as disclosed in US 5,216,167 and US 5,312,924.

The process for the preparation of crystalline Form-II (recrystallised from toluene) is disclosed in our co-pending Indian patent application (sent to IPO, Chennai on August 22, 2002).

The present invention is described in detail with examples given below that are provided by the way of illustration only and therefore, should not be construed to limit the scope of invention.

I) Preparation of Novel Crystalline Form-III of (S)-Repaglinide:

EXAMPLE-1:

Crude (S)-Repaglinide (5.0 grams) was dissolved in dichloromethane (10 ml) at an ambient temperature. The reaction mixture was stirred to get a clear solution. Petroleum ether (30 ml) was added and then cooled to a temperature of 0-5°C. The reaction mixture was stirred for 1 hour to get solid separation. The obtained solid was filtered, washed

with petroleum ether (10.0 ml) and dried at a temperature of 50–55 ° C to result the novel crystalline Form-III of S-Repaglinide.

(Weight: 4.0 grams, Melting range: 80-84°C, M.C by KF: 0.35%).

EXAMPLE-2:

Crystalline Form-I of (S)-Repaglinide [recrystallised from acetone and petroleum ether] (10.0 grams) was dissolved in dichloromethane (20 ml) at an ambient temperature. The reaction mixture was stirred to get a clear solution. Petroleum ether (60 ml) was added and then cooled to a temperature of 0-5°C. The reaction mixture was stirred for 1 hour to get solid separation. The obtained solid was filtered and washed with Petroleum ether (20.0 ml) and dried at a temperature of 50–55 ° C to result the novel crystalline Form-III of S-Repaglinide.

(Weight: 9.2 grams, Melting range: 80-84°C, M.C by KF: 0.25%).

EXAMPLE-3:

Crystalline Form-I of (S)-Repaglinide [recrystallised from aqueous ethanol] (10.0 grams) was dissolved in dichloromethane (20 ml) at an ambient temperature. The reaction mixture was stirred to get a clear solution. Petroleum ether (60 ml) was added and then cooled to a temperature of 0-5°C. The reaction mixture was stirred for 1 hour to get solid separation. The obtained solid was filtered and washed with Petroleum ether (20.0 ml) and dried at a temperature of 50–55 ° C to result the novel crystalline Form-III of S-Repaglinide.

(Weight: 7.8 grams, Melting range: 80-84°C, M.C by KF: 0.26%).

EXAMPLE-4:

Crystalline Form-II of (S)-Repaglinide [recrystallised from toluene and petroleum ether] (5.0 grams) was dissolved in dichloromethane (10 ml) at an ambient temperature. The reaction mixture was stirred to get a clear solution. Petroleum ether (30 ml) was added and then cooled to a temperature of 0-5°C. The reaction mixture was stirred for 1 hour to get solid separation. The obtained solid was filtered and washed with Petroleum ether (10.0 ml) and dried at a temperature of 50–55 °C to result the novel crystalline Form-III of S-Repaglinide.

(Weight: 4.8 grams, Melting range: 80-83°C, M.C by KF: 0.2%).

EXAMPLE-5:

Crystalline Form-II of (S)-Repaglinide [recrystallised from toluene] (20.0 grams) was dissolved in dichloromethane (40 ml) at an ambient temperature. The reaction mixture was stirred to get a clear solution. Petroleum ether (120 ml) was added and then cooled to a temperature of 0-5°C. The reaction mixture was stirred for 1 hour to get solid separation. The obtained solid was filtered and washed with Petroleum ether (40.0 ml) and dried at a temperature of 50–55 °C to result the novel crystalline Form-III of S-Repaglinide.

(Weight: 19.2 grams, Melting range: 80-84°C, M.C by KF: 0.3%).

EXAMPLE-6:

Amorphous form of (S)-Repaglinide (10.0 grams) was dissolved in dichloromethane (20 ml) at an ambient temperature. The reaction mixture was stirred to get a clear solution. Petroleum ether (60 ml) was added and then cooled to a temperature of 0-5°C. The

reaction mixture was stirred for 1 hour to get solid separation. The obtained solid was filtered and washed with Petroleum ether (20.0 ml) and dried at a temperature of 50–55 °C to result the novel crystalline Form-III of S-Repaglinide. (Weight: 8.6 grams, Melting range: 79-84°C, M.C by KF: 0.20%).

II) Preparation of Novel Amorphous form of (S)-Repaglinide

EXAMPLE-7:

Dissolved the crystalline Form-I [recrystallised from acetone and petroleum ether] of (S)-Repaglinide (6.0 grams) in methanol (20.0 ml) and heated to a temperature of 45-50°C till clear solution results. Then the reaction solution was cooled to a temperature of 0-5°C and stirred till the solid separates. The separated solid was filtered, washed with methanol (12.0 ml) and dried at a temperature of 50-60°C under vacuum to yield the desired novel amorphous form of (S)-Repaglinide.

(Weight: 5.4 grams, Melting range: 74 -77°C, M.C by KF: 0.82%).

EXAMPLE-8:

Dissolved the crystalline Form-II [recrystallised from toluene and petroleum ether] of (S)-Repaglinide (10.0 grams) in methanol (34.0 ml) and heated to a temperature of 45-50°C till clear solution results. Then the reaction solution was cooled to a temperature of 0-5°C and stirred till the solid separates. The separated solid was filtered, washed with methanol (20.0 ml) and dried at a temperature of 50-60°C under vacuum to yield the desired novel amorphous form of (S)-Repaglinide.

(Weight: 9.4 grams, Melting range: 74 -76°C, M.C by KF: 0.01%).

EXAMPLE-9:

Dissolved the crystalline Form-II [recrystallised from toluene] of (S)-Repaglinide (20.0 grams) in methanol (67.0 ml) and heated to a temperature of 45-50°C till clear solution results. Then the reaction solution was cooled to a temperature of 0-5°C and stirred till the solid separates. The separated solid was filtered, washed with methanol (40.0 ml) and dried at a temperature of 50-60°C under vacuum to yield the desired novel amorphous form of (S)-Repaglinide.

(Weight: 18.2 grams, Melting range: 73 -76°C, M.C by KF: 0.90%).

EXAMPLE-10:

Dissolved the crystalline Form-III of (S)-Repaglinide (20.0 grams) in methanol (67.0 ml) and heated to a temperature of 45-50°C till clear solution results. Then the reaction solution was cooled to a temperature of 0-5°C and stirred till the solid separates. The separated solid was filtered, washed with methanol (40.0 ml) and dried at a temperature of 50-60°C under vacuum to yield the desired novel amorphous form of (S)-Repaglinide.

(Weight: 17.2 grams, Melting range: 74 -77°C, M.C by KF: 0.92%).

DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWINGS:

Fig.1 is characteristic X-ray powder diffraction pattern of novel crystalline Form-III of (S)-Repaglinide.

Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

The significant 2-theta values obtained are 4.438, 6.811, 7.803, 9.277, 11.091, 11.888, 12.918, 13.464, 14.342, 15.766, 16.236, 17.081, 18.060, 18.747, 19.251, 19.594, 19.995, 20.339, 21.185, 21.960, 22.180, 22.581, 23.235, 23.767, 24.080, 25.020, 25.315, 25.780, 26.675, 27.388, 28.028, 30.255, 35.500, 38.739 two-theta degrees.

Fig.2 is characteristic Differential Scanning Colorimetry thermogram of novel crystalline Form-III of (S)-Repaglinide.

Vertical axis: Heat flow (mW); Horizontal axis: Temperature ($^{\circ}$ C).

The Differential Scanning Calorimetry thermo gram exhibits a significant endo peak around 80°C .

Fig.3 is characteristic Infrared absorption spectrum of novel crystalline Form-III of (S)-Repaglinide.

Vertical axis: Transmission (%); Horizontal axis; Wave number (Cm^{-1}).

The identified significant Infrared bands are around 3291, 3029, 2935, 2795, 1292, 1727, 1643, 1611, 1537, 1436, 1225, 1171, 1087, 1028, 986, 922, 860, 764, 686 and 533 cm^{-1} .

Fig. 4 is characteristic X-ray powder diffraction pattern of novel amorphous form of (S)-Repaglinide.

Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

It shows a plain halo with no peaks, which is characteristic of the amorphous nature of product.

We claim:

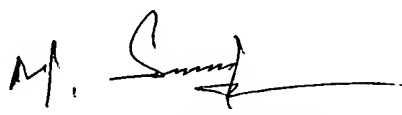
1. Novel crystalline Form-III of (S)-2-Ethoxy-4- [N- (1-(2-piperidino-phenyl)-3-Methyl-1-butyl)-amino carbonyl methyl] benzoic acid [(S)-Repaglinide)].
2. The novel crystalline Form-III of (S)-Repaglinide of claim 1 having X-ray powder diffraction pattern with peaks around 4.438, 6.811, 7.803, 9.277, 11.091, 11.888, 12.918, 13.464, 14.342, 15.766, 16.236, 17.081, 18.060, 18.747, 19.251, 19.594, 19.995, 20.339, 21.185, 21.960, 22.180, 22.581, 23.235, 23.767, 24.080, 25.020, 25.315, 25.780, 26.675, 27.388, 28.028, 30.255, 35.500, 38.739 two-theta degrees.
3. The novel crystalline Form-III of (S)-Repaglinide according to claim 2, which provides X-ray diffraction pattern substantially in accordance with Figure (1).
4. The novel crystalline Form-III of (S)-Repaglinide according to claim 1 having a Differential Scanning Colorimetry thermogram, which exhibits a significant endo peak around 80°C.
5. The novel crystalline Form-III of (S)-Repaglinide according to claim 4 having a Differential Scanning Colorimetry thermogram substantially in accordance with Figure (2).
6. The novel crystalline Form-III of (S)-Repaglinide according to claim 1 having an identified characteristic Infrared bands around 3291, 3029, 2935, 2795, 1292, 1727, 1643, 1611, 1537, 1436, 1225, 1171, 1087, 1028, 986, 922, 860, 764, 686 and 533 cm⁻¹.
7. The novel crystalline Form-III of (S)-Repaglinide according to claim 6 having an Infrared spectrum substantially in accordance with Figure (3).

8. A process for preparing the novel amorphous of (S)-repaglinide, which comprises;
- i. dissolving (S)-Repaglinide in C₁-C₃ haloalkane solvent;
 - ii. adding C₅-C₇ aliphatic or alicyclic hydrocarbon solvent as anti-solvent to the solution of step (i) to precipitate the solid;
 - iii. isolating the precipitated solid obtained in step (ii) to afford the novel crystalline Form-III of (S)- Repaglinide;
9. The process according to step (i) of claim 8, wherein the (S)-Repaglinide is selected from (S)-Repaglinide crude, (S)-Repaglinide crystalline Form-I, (S)-Repaglinide Form-II or an amorphous form of (S)-Repaglinide.
10. The process according to step (i) of claim 8, wherein the C₁-C₃ haloalkane solvent is selected from dichloromethane, chloroform or dichloroethane.
11. The process according to claim 10, wherein the preferred haloalkane solvent is dichloromethane.
12. The process according to step (ii) of claim 8, wherein the C₅-C₇ aliphatic or alicyclic hydrocarbon solvent is selected from petroleum ether, hexane, n-heptane, cyclohexane or cyclo heptane.
13. The process according to step 12, wherein the preferred aliphatic hydrocarbon solvent is petroleum ether.
14. Novel amorphous form of (S)-2-Ethoxy-4- [N- (1-(2-piperidino-phenyl)-3- methyl-1-butyl)-amino carbonyl methyl) benzoic acid [(S)-Repaglinide)].

15. The novel amorphous form of (S)-Repaglinide of claim 14 which is characterized by powder X-ray diffractogram.
16. The amorphous form of (S)-Repaglinide according to claims 14 and 15, which provide X-ray powder diffraction pattern substantially in accordance with Figure (4).
17. A process for preparing the novel amorphous form of (S)-repaglinide, which comprises;
 - a) dissolving crystalline form of (S)-Repaglinide in C₁-C₄ straight or branched chain alcoholic solvents at a temperature of 35-70 °C, preferably at 45-55 °C;
 - b) cooling the reaction solution of step (a) to a temperature of 0-5°C;
 - c) stirring the reaction solution of step (b) till the solid substantially separates;
 - d) filtering the separated solid obtained in step (c) by conventional methods;
 - e) drying the resulting solid of step (d) under vacuum at a temperature of 40 to 70°C to a constant weight to afford the desired novel amorphous form of (S)- Repaglinide.
18. The process according to claim 17, where in the (S)-Repaglinide is selected from (S)-Repaglinide crystalline Form-I, (S)-Repaglinide Form-II or (S)-Repaglinide Form-III.
19. The process according to step (a) claim of 17, wherein the C₁-C₄ alcohol is selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol and tertiary butanol.
20. The process according to claim 19, where in the preferred alcohol is methanol.

21. The processes for the preparation of novel crystalline Form-III and novel amorphous form of (S)-Repaglinide are substantially as herein described and exemplified.

Dated 28th day of August, 2002

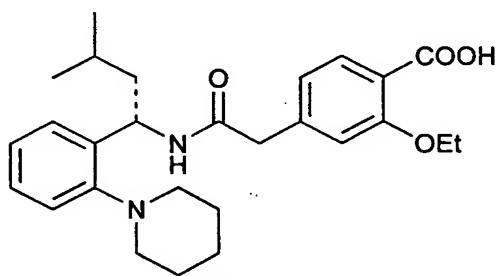
Signed) 
Dr. Manne Satyanarayana Reddy,
Vice-President (R&D),
Dr. Reddy's Laboratories Limited.

ABSTRACT

Title of the Invention: "Novel forms (S)-Repaglinide and a Process for Preparation thereof"

The present invention relates to novel forms of (S)- Repaglinide.

More specifically, the present invention relates to novel crystalline Form-III and novel amorphous form of (S)- Repaglinide. The present invention also relates to processes for the preparation thereof. Chemically (S)-Repaglinide is (S)-2-Ethoxy-4- [N- (1-(2-piperidino-phenyl)-3-methyl-1-butyl)-amino carbonyl methyl] benzoic acid having the following Formula (1).



Formula (1)

The process for preparation of crystalline Form-III comprises dissolution of (S)-Repaglinide crude, (S)-Repaglinide crystalline Form-I, (S)-Repaglinide Form-II or (S)-Repaglinide amorphous in a C₁-C₃ haloalkane solvent at an ambient temperature followed by diluting with an excess volume of C₅-C₁₀ aliphatic or alicyclic hydrocarbon solvent under stirring to isolate the desired novel crystalline Form-III of (S)-Repaglinide.

The process for preparation of novel amorphous form of (S)-Repaglinide comprises the recrystallisation of crystalline Form-I, Form-II and Form-III of (S)-Repaglinide in C₁-C₄ straight or branched chain alcohol solvent.

The processes of the present invention are simple, non-hazardous and commercially viable over prior art processes.

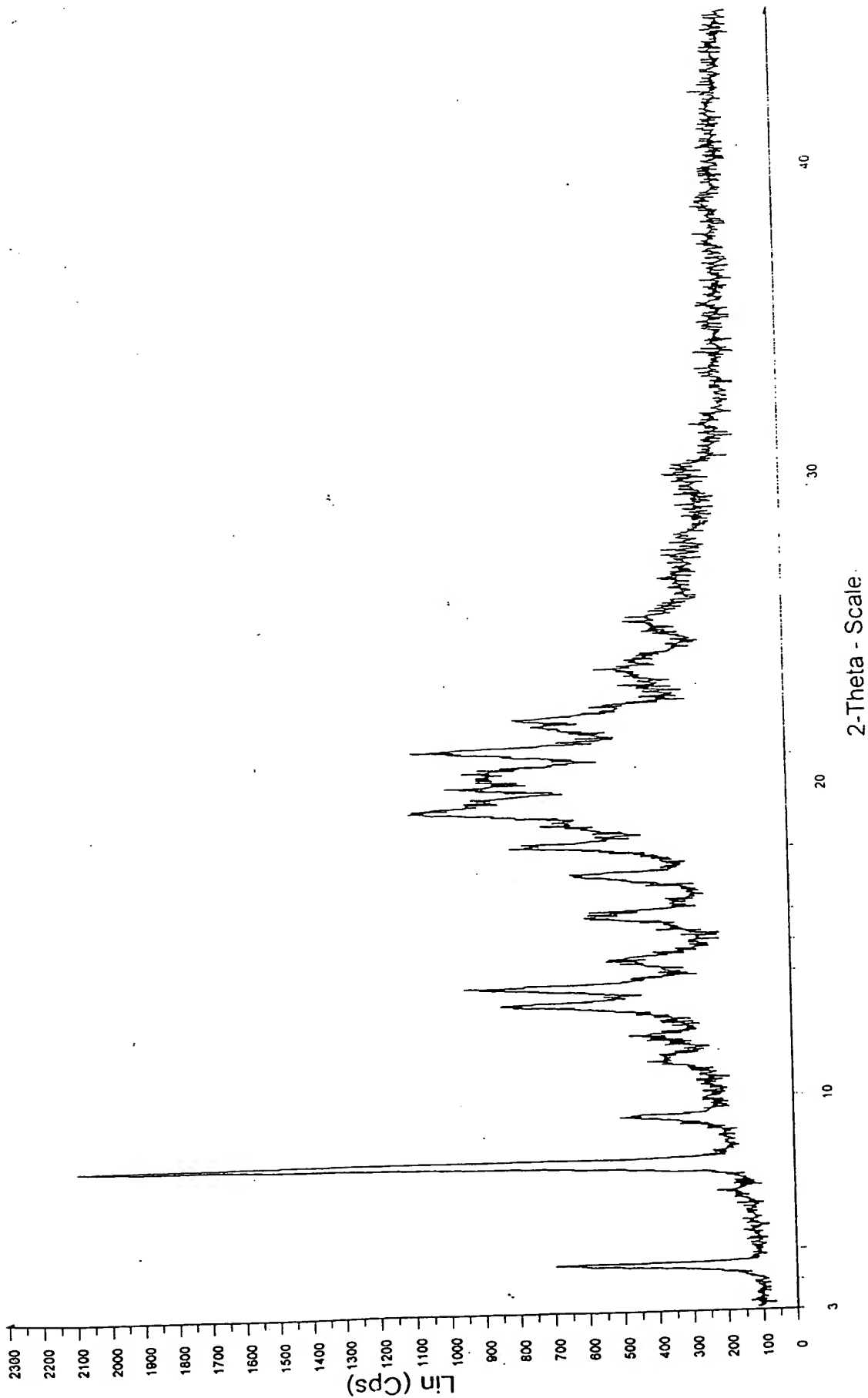


Fig. 1

ORIGINAL
30 AUG 2002 6.37 AM
MANNE SATYANARAYANA REDDY
Dr. Reddy's



K. S. S.
MANNE SATYANARAYANA REDDY

ORIGINAL

2007 03 09 10:00 AM

Fig. 2007 03 09 10:00 AM



MANNE SATYANARAYANA REDDY

65-15348-100

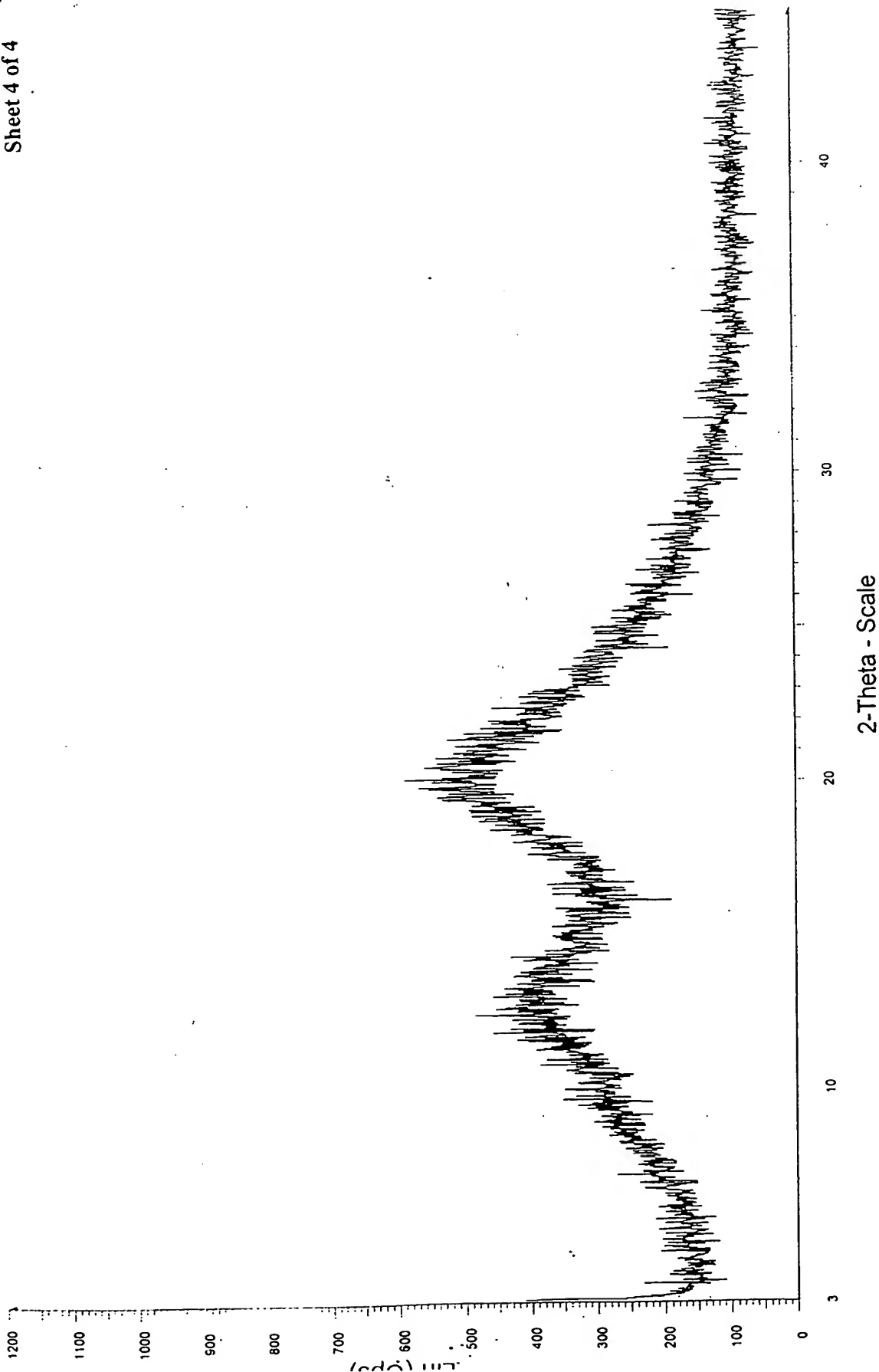


Fig. 4

M. Sanyal

MANNE SATYANARAYANA REDDY

ORIGINAL
12-11-2010